

Study 4

**Acute Oral Toxicity Study in Rats,
October 14, 1998**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**"ACUTE ORAL TOXICITY
STUDY IN RATS"**

[REDACTED] EXP. No [REDACTED]

EEC Guidelines (B.1)
OECD Guidelines (401)

Issued on October 14, 1998

SPONSOR

[REDACTED]

PERFORMING LABORATORY

[REDACTED]

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[REDACTED]

Exp. No. [REDACTED]

TITLE OF THE STUDY

"Acute oral toxicity study in rats treated with the test article [REDACTED]
[REDACTED]

PURPOSE OF THE STUDY

The purpose of the study was to evaluate the acute oral toxicity of the test article
[REDACTED]

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[REDACTED]
Exp. No. [REDACTED]

FOREWORD

On behalf of [REDACTED], authorized by the [REDACTED] Health Authorities (1-2) to conduct safety studies, has performed an acute toxicity study by oral route in Sprague Dawley Crl: CD(SD) BR rats ([REDACTED] Experiment No. [REDACTED]), with the test article:

[REDACTED]

A sample of the substance used, along with pertinent documentation, is held in sufficient quantity in the [REDACTED] archives and is at the disposal of the Ministero della Sanità.

The undersigned declares that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantees the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.


Dr. [REDACTED]

Scientific and Operative Director

Ivrea, October 14, 1998

- (1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974
- (2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

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[REDACTED]

[REDACTED] Exp. No. [REDACTED]

QUALITY ASSURANCE STATEMENT

[REDACTED] Experiment number: [REDACTED]

Study title:

"Acute oral toxicity study in rats treated with the test article [REDACTED]"
[REDACTED]

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the study director and to facility management.

This study was inspected on:

Dates of inspection/audit

May 29, 1998
October 12 - 13, 1998

Dates of report to
Study Director and Management

May 29, 1998
October 13, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit:

October 15, 1998

[REDACTED]

Head of Quality Assurance Unit

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[REDACTED]
[REDACTED] Exp. No. [REDACTED]

CERTIFICATION OF GLP COMPLIANCE

Study No. [REDACTED] entitled :

"Acute oral toxicity study in rats treated with the test article [REDACTED]
[REDACTED]"

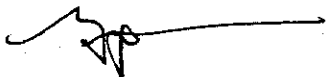
I hereby confirm that this study was conducted in accordance with the OECD [C(81) 30 (final)], Principles of Good Laboratory Practice (GLP).

The Sponsor is responsible for GLP compliance of any information supplied.

These principles were adopted by the EEC and incorporated into EEC Directive 88/320, that was legally enforced by the [REDACTED] Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

The final report fully and accurately reflects the raw data generated during the conduct of the study.

This report consists of 39 pages.



Study Director

Dr. [REDACTED]

Ivrea, October 21, 1998

[REDACTED]

Exp. No. [REDACTED]

SCIENTISTS INVOLVED IN THE STUDY

Study No. [REDACTED]

"Acute oral toxicity study in rats treated with the test article [REDACTED]
[REDACTED]"

Study Director

Dr. [REDACTED]

Senior Scientist for General
Toxicology

Dr. [REDACTED]

Head of General Toxicology I Unit

Dr. [REDACTED]

Centralized Pharmacy Head

Dr. [REDACTED]

Pharmacy Service Head

Dr. [REDACTED]



Exp. No.

MATERIALS AND METHODS

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[REDACTED]
[REDACTED] Exp. No. [REDACTED]

EXPERIMENTAL DESIGN

[REDACTED] Experiment No.: [REDACTED]

Test article: [REDACTED]

Administration route: oral (by gavage)

Duration of treatment period: single administration

Duration of post-treatment
observation period: 14 days

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guidelines (section 4, subpart 401, Paris 1981 and subsequent revisions).

TEST SYSTEM

Species, strain and Sprague Dawley Crl: CD (SD) BR rat
substrain:

Justification for selection of
the test system : the Sprague Dawley rat was chosen as rodent species since it is an appropriate experimental model widely accepted by Health Authorities, with documented susceptibility to a wide range of toxic substances

Number and sex of animals: 5 males/dose at the doses of 126 and 162 mg/kg
5 males and 5 females at the dose of 90 mg/kg

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Exp. No. [redacted]

Supplier: [redacted]
[redacted]
[redacted]

Shipping slips Nos. 04120 (June 5, 1998), 04317 (June 12, 1998), 04635 (June 26, 1998) and 04980 (July 10, 1998)

Age (at randomization): no more than three months

Body weight (at randomization):
Males: 273-350 g
Females: 211-269 g

Acclimatization: at least 5 days before the start of the test.
Animals were observed daily to ascertain their fitness for the study.

Housing: 5 animals/sex/cage in air-conditioned room.
- Temperature: $22^{\circ}\text{C} \pm 2$
- Relative humidity: $55\% \pm 10$
- Air changes: about 20 / hour filtered on HEPA 99.97%
- Light: 12 hour cycle (7 a.m. - 7 p.m.)
- Cage size: grill cages 40.5x38.5x18h cm with stainless steel feeder. The waste that dropped through the grill bottom onto removable paper was periodically disposed of.

Animal identification: by appropriately coloring different areas of the limbs.
Cage card gave experiment number, dosage group, sex and date of administration.

Diet: GLP 4RF21 top certificate pelleted diet produced by [redacted] feed licensee [redacted]
[redacted] The declared contents on the label, on dry matter basis (moisture 12%), were:

crude protein	18.50%
crude fat	3.00%
crude fiber	6.00%
crude ash	7.00%

[REDACTED]

[REDACTED] Exp. No. [REDACTED]

The diet was supplemented by the Producer with vitamins and trace elements. The Producer supplies a certificate of analysis for nutrients and contaminants, the levels of which are within the limits proposed by EPA-TSCA (44FR:44053-44093, July 26, 1979).

[REDACTED] has the animal feed re-analyzed at least twice a year for bacterial contamination.

The diet was available "ad libitum" to the animals.

Water:

from the municipal water main system.

Water is filtered and distributed "ad libitum" to the animals by an automatic valve system.

Periodically drinking water is analyzed for microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physical characteristics. The accepted limits of quality of the drinking water were those defined in EEC directive 80/778

Contaminants that might interfere with the objectives of the study were not expected to be present in the diet or drinking water.

TEST ARTICLE, CHARACTERIZATION

Identification:	[REDACTED]
Batch:	[REDACTED]
Characteristics:	white powder
Purity:	> 99%
Manufacturing date:	March 30, 1998
Expiry date:	December 2000
Storage conditions:	at room temperature

VEHICLE CHARACTERIZATION

Deionized water

TEST ARTICLE FORMULATE PREPARATION

When required, an exact amount of test article was weighed in a suitable graduated container and made up to final volume with vehicle to obtain the concentration required.

When the formulates were suspension they were kept magnetically stirred until the end of administration and were administered within one hour of the preparation.

TEST DESCRIPTION

Administration route: oral (by gavage)

Reason for selection of
administration route: possible ingestion by humans

Experimental design:

Dose*	Treated	Treatment	Final
mg/kg	animals	Date	killing
162	5 males	July 15, 1998	Found dead
126	5 males	August 14, 1998	September 4, 1998
90	5 males	July 28, 1998	August 18, 1998
90	5 females	August 20, 1998	September 3, 1998

*The doses were defined on the basis of a preliminary study.

Administration method: The volume of administration was 10 ml/kg defined on the basis of the individual body weight. The administration was done by gavage to rats which had been fasted about 16 hours. Feed was returned to the rats about three hours after the test article administration.

Observation period: 14 or 21 *days after administration
* for males in groups of 90 and 126 mg/kg due to the delayed clinical changes.

Observation of clinical signs and mortality: at 30 minutes, 2, 4 and 6 hours on the first day after the administration (day 1) and then twice a day up to termination of the observation period



Body weight: twice pre-trial (at randomization and on day 1 just before administration) and on days 3, 8 and 14. On day 1 the animals were weighed after a 16-hour fasting period. For the males in groups of 90 and 126 mg/kg body weights were also recorded on day 21.

Gross pathology: on animals which died before the end of the study and on animals killed (fasted overnight) by excision of the femoral arteries, after i.p. overdosage anesthesia with 5% sodium pentobarbital, at the end of the observation period


Histology: portions of abnormal entities found in the necropsied animals were collected. The tissue samples were fixed and preserved in 10% buffered formalin. Histologic examination was not performed

LD₅₀ and its statistical limits: LD₅₀ was calculated by the method of the Probit (Bliss - Finney) - A.P. Rosiello et al., J. Tox. and Env. Health, 3: 797-809, 1977.

RECORD FILING

The protocol, a reserve sample of the batch of the test article used, the raw data bound in a register numbered , the specimens, the final report and all other documents pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, analysis of diet and water are filed at  premises for ten years from the issue date of this report and then sent to the Sponsor.



PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the  Standard Operating Procedures (SOP's) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the Italian D. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accommodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.


Exp. No. 

RESULTS

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CLINICAL OBSERVATIONS

MORTALITY (TABLE I)

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	90	126	162
Treated animals	5M+5F	5M	5M
Mortality	0	3M	5M
Total (%)	0%	60%	100%

The deaths occurred 5-14 days after dosing, with the first case observed on day 5 after administration in the 162 mg/kg group.

No deaths occurred in the animals of either sex in the lowest dose group (90 mg/kg).

Even though the LD₅₀ was not calculable with the Probit method, the approximate LD₅₀ could be considered 120 mg/kg (with 0% mortality at 90 mg/kg and 100% mortality at 162 mg/kg).

CLINICAL SIGNS (TABLE 2 AND APPENDIX I)

Hypoactivity, piloerection and hunched posture were observed in the males of the various dose groups, starting 3-4 days (162 mg/kg group) or 4-11 days (the lower doses) after dosing. One male of the 126 mg/kg group showed also abdominal dilatation during the latter stage of the observation period.

Piloerection was the only clinical change observed in the females received the test article at the lowest dose (6-11 days after treatment).

Complete or partial recovery was achieved at the end of the observation period in the surviving animals.

BODY WEIGHT (*APPENDIX 2*)

Decrease in body weight or retarded growth was found in animals given the various doses during the observation period.

POST-MORTEM EXAMINATION

GROSS PATHOLOGY (*TABLE 3 AND APPENDIX 3*)

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness, erosion and congestion of stomach, intestine congestion and decreased size of spleen. The two latter changes were mainly confined to animals of the highest dose group (162 mg/kg). Moreover, kidney medulla congestion or pale kidney was seen in a few animals.

At the autopsy carried out at the end of the observation period, no appreciable macroscopic findings were evident in any rat.

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SUMMARY AND CONCLUSIONS

Experimental data from a toxicity study in which Sprague Dawley CrI:CD(SD) BR rats received oral administration of the test article [REDACTED] are given in this report.

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guideline (section 4, subpart 401, Paris 1981 and subsequent revisions).

The test article was administered to the rats as a suspension or solution (depending on the concentration of the test article in the vehicle) in deionized water at the dosages of 90, 126 and 162 mg/kg to groups of 5 males/dose and at the dose of 90 mg/kg to 5 females for confirmation in the other sex. All rats were treated after a 16-hour fasting period. The day of treatment was considered day 1 of the study. The animals were weighed twice before treatment (at randomization and on day 1 just before treatment) and on days 3, 8 and 14 (surviving males in the 90 and 126 mg/kg groups were also weighed on day 21). They were clinically observed for 14 or 21 days following the treatment. Macroscopic examinations were performed in the animals which died before the end of the study. At the end of the observation period the surviving rats were killed (fasted overnight) by excision of the femoral arteries after i.p. overdosage anesthesia with 5% sodium pentobarbital and were subjected to a thorough autopsy.

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	90	126	162
Treated animals	5M+5F	5M	5M
Mortality	0	3M	5M
Total (%)	0%	60%	100%

The deaths occurred 5-14 days after dosing, with the first case observed on day 5 after administration in the 162 mg/kg group.

No deaths occurred in the animals of either sex in the lowest dose group (90 mg/kg).

Even though the LD₅₀ was not calculable with the Probit method, the approximate LD₅₀ could be considered 120 mg/kg (with 0% mortality at 90 mg/kg and 100% mortality at 162 mg/kg)

Hypoactivity, piloerection and hunched posture were observed in the males of the various dose groups, starting 3-4 days (162 mg/kg group) or 4-11 days (the lower doses) after dosing. One male of the 126 mg/kg group showed also abdominal dilatation during the latter stage of the observation period. Piloerection was the only clinical change observed in the females that received the test article at the lowest dose (6-11 days after treatment). Complete or partial recovery was achieved at the end of the observation period in the surviving animals. Moreover, decrease in body weight or retarded growth was found in animals given the various doses during the observation period.

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness, erosion and congestion of stomach, intestine congestion and decreased size of spleen. The two latter changes were mainly confined to animals of the highest dose group (162 mg/kg). At the autopsy carried out at the end of the observation period, no appreciable macroscopic findings were evident in any rat.

In conclusion, the approximate LD₅₀ of the test article [REDACTED], when administered to rats by oral route, was 120 mg/kg. The compound induced delayed toxicity (liver and stomach were involved) mainly in animals given the higher doses.

Dr. [REDACTED]

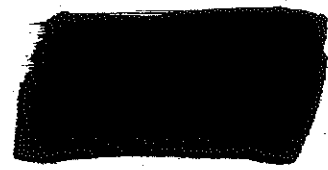
Study Director

October 14, 1998

Dr. [REDACTED]

Senior Scientist for General Toxicology

Oct. 14, 1998



Exp. No.

GROUP DATA

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Test article: [REDACTED]
 Title : Acute oral toxicity study in rats
 exp. : [REDACTED]

TABLE 1. - Mortality and LD50 calculation (p. 1)

Males - Females

Dose (mg/kg)	90	126	162
Treated animals	10	5	5
Day 5	0	0	1
7	0	0	1
8	0	0	1
9	0	0	1
10	0	0	1
14	0	3	0
Total no. (day 21)	0	3	5
Total (%)	0.0%	60.0%	100.0%

LD50 not calculable

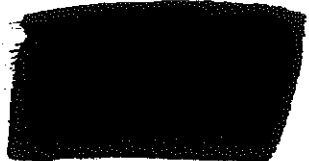
124

Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

TABLE 2. - Clinical signs (maximum daily frequency) (p. 1)
(no. of animals affected, from-to)

	Males		
	Dose (mg/kg)	90	126 162
no. of treated animals		5	5 5
Death		-	3 5d-10d
Hypoactivity		2 8d-10d	5 11d-14d 3 4d- 9d
Piloerection		5 4d-16d	5 4d-21d 5 3d- 9d
Hunched posture		3 4d-10d	5 5d-13d 4 3d- 9d
Abdominal dilatation		-	1 16d-21d -
Recovery		5 17d	- -

- (not observed) from-to (first-last observation in one or more animals)
Time : d (days)



Test article: [REDACTED]
 Title : Acute oral toxicity study in rats
 exp. : [REDACTED]

TABLE 2. - Clinical signs (maximum daily frequency) (p. 2)
 (no. of animals affected, from-to)
 Females

Dose (mg/kg)	90
no. of treated animals	5
Piloerection	5 6d-11d
Recovery	5 12d

from-to (first-last observation in one or more animals)
 Time : d (days)

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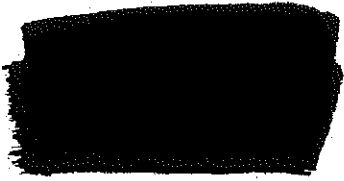
Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

TABLE 3. - Gross pathology examination (p. 1)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an.		Males	
Dose (mg/kg)		90	126 162
no. of animals		0	3 5
no. of animals without appreciable lesions		0	0 0
General observation			
cannibalized		1 33.33%	1 20.00%
Kidneys			
pale		1 1(2.0) 33.33%	0
medulla, congestion		0	2 2(2.0) 40.00%
Liver			
pale		2 2(2.5) 66.67%	4 4(2.0) 80.00%
Spleen			
decreased size		0	4 4(2.8) 80.00%

- (not examined)
Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

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Test article:
 Title : Acute oral toxicity study in rats
 exp. :

TABLE 3. - Gross pathology examination (p. 2)
 (no. of cases, mean severity, %)

Dead or agonal sacrificed an.		Males	
Dose (mg/kg)		90	126
			162
no. of animals		0	3
no. of animals without appreciable lesions		0	0
			0
Stomach			
congestion		-	0
			3(2.0)
			60.00%
erosion		-	0
			1(2.0)
			20.00%

- (not examined)
 Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

Test article: [REDACTED]
 Title : Acute oral toxicity study in rats
 exp. : [REDACTED]

TABLE 3. - Gross pathology examination (p. 3)
 (no. of cases, mean severity, %)

Final killing	Males		
	Dose (mg/kg)		
	90	126	162
no. of animals	5	2	0
no. of animals without appreciable lesions	5	2	0
.....

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Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

TABLE 3. - Gross pathology examination (p. 4)
(no. of cases, mean severity, %)

Final killing		Females
Dose (mg/kg)	-----	90
no. of animals		5
no. of animals without appreciable lesions		5
.....	

Exp. No.

APPENDICES

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APPENDIX 1. - Clinical signs incidence (p. 1)
(no. of animals affected)

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Cage #	8F	Day Time	1	2	3	4	5	6	7	8	9	10	11	12	13	14
		30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M
No clinical signs		5	5	5	5	5	5	5	5	5	3	3	3	3	5	5
Piloerection		5	5	5	5	5	5	5	5	5	2	2	2	2	2	2

Time: m (minutes) h (hours) M (morning) A (afternoon)

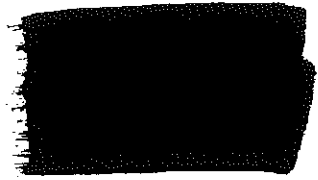
Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

APPENDIX 1. - Clinical signs incidence (p. 2)
(no. of animals affected)

Dose (mg/kg)		126																
Cage #	9M	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
		Time 30m 2h 4h 6h	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA	MA
Death		5	5	5	5	5												
No clinical signs												5	5	5	5	5	5	5
Hypoactivity												5	5	5	5	5	5	5
Piloerection												5	5	5	5	5	5	5
Hunched posture												5	5	5	5	5	5	5
Abdominal dilatation																	1	1

Cage #	9M	Day 18	19	20	21
	(follows)	Time MA	MA	MA	MA
Piloerection		2	2	2	2
Abdominal dilatation		1	1	1	1

Time: m (minutes) h (hours) M (morning) A (afternoon)



Test article: [redacted]
Title: Acute oral toxicity study in rats
exp. [redacted]

APPENDIX 1. - Clinical signs incidence (p. 3)
(no. of animals affected)

Dose (mg/kg)	162										
Cage #	5M	Day 1	2	3	4	5	6	7	8	9	10
		Time 30m 2h 4h 6h	M A	M A	M A	M A	M A	M A	M A	M A	M
Death						1		1	1	1	1
No clinical signs		5	5	5	5	5					
Hypoactivity						1		3	3	2	1
Piloerection				5	5	4	4	4	4	3	2
Hunched posture				1	1	1	1	4	3	2	1

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Time: m (minutes) h (hours) M (morning) A (afternoon)

Test article: [REDACTED]
 Title: Acute oral toxicity study in rats
 exp. [REDACTED]

APPENDIX 2. - Body weight (g) (p. 1)
 (individual)

Dose (mg/kg)		90										
Animal #		31M	32M	33M	34M	35M	36F	37F	38F	39F	40F	
Week	day											
	0	300	305	301	324	350	261	269	248	211	238	
1	1	274	286	280	306	319	270	275	250	218	248	
1	3	260	275	260	295	317	262	276	245	214	244	
2	8	222	251	211	269	260	250	269	240	217	240	
2	14	215	283	237	212	275	293	297	263	233	261	
3	21	258	343	279	252	298						

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Exp. No. [REDACTED]

Test article: [REDACTED]
Title : Acute oral toxicity study in rats
exp. : [REDACTED]

APPENDIX 2. - Body weight (g) (p. 2)
(individual)

Dose (mg/kg)		126				
		Animal #				
		41M	42M	43M	44M	45M
Week	day					
	0	289	287	312	280	306
1	1	267	254	282	253	274
1	3	252	251	282	268	279
2	8	233	248	269	280	251
2	14		254		293	
3	21		314		348	

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Exp. No. [REDACTED]

Test article: [REDACTED]
Title : Acute oral toxicity study in rats
exp. : [REDACTED]

APPENDIX 2. - Body weight (g) (p. 3)
(individual)

Dose (mg/kg)		162				
		21M	22M	23M	24M	25M
Animal #	Week day					
0		277	333	320	320	273
1	1	252	311	294	292	294
1	3	234	299	280	289	232
2	8	164			216	

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Test article: [REDACTED]
Title : Acute oral toxicity study in rats
exp. : [REDACTED]

APPENDIX 3. - Gross pathology examination (p. 1)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 126

An#	Death day/code#	T I S S U E	Gross observations
41M 14	M2	General observation	cannibalized
43M 14	M2	Liver	pale, diffuse, moderate
45M 14	M2	Kidneys	pale, diffuse, moderate
		Liver	pale, diffuse, severe

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Death code : M2 (Natural death)

Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 2)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 162

An#	Death day/code#	T I S S U E	Gross observations
21M	10 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, severe
22M	8 M2	Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, severe
		Stomach	congestion, diffuse, moderate erosion, multifocal, moderate
23M	7 M2	Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, moderate
		Stomach	congestion, diffuse, moderate
24M	9 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, severe
		Stomach	congestion, diffuse, moderate

Death code : M2(Natural death)

139

Exp. No. [redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 3)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 162

An#	Death	T I S S U E	Gross observations
-----	day/code#	-----	-----
25M	5	M2	General observation cannibalized

Death code : M2(Natural death)

1760

Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 4)
(individual)

Final Killing

Dose (mg/kg) 90

An#	Death day	T I S S U E	Gross observations
31M	22	General observation	no macroscopically appreciable lesions
32M	22	General observation	no macroscopically appreciable lesions
33M	22	General observation	no macroscopically appreciable lesions
34M	22	General observation	no macroscopically appreciable lesions
35M	22	General observation	no macroscopically appreciable lesions
36F	15	General observation	no macroscopically appreciable lesions
37F	15	General observation	no macroscopically appreciable lesions
38F	15	General observation	no macroscopically appreciable lesions
39F	15	General observation	no macroscopically appreciable lesions
40F	15	General observation	no macroscopically appreciable lesions

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Test article: [redacted]
Title : Acute oral toxicity study in rats
exp. : [redacted]

APPENDIX 3 - Gross pathology examination (p. 5)
(individual)

Final killing

Dose (mg/kg) 126

An#	Death day	T I S U E	Gross observations
42M	22	General observation	no macroscopically appreciable lesions
44M	22	General observation	no macroscopically appreciable lesions

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